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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/480,236
Filing Date: January 10, 2000
Appellant(s): DIGAN ET AL.

Thomas R. Savitsky
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 3/09/04 appealing from the Office action mailed 11/21/02.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is substantially correct. Appellant's description of the asserted usefulness of the claimed product is not appropriate for this section of the Brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

U.S. Patent No. 6,103,235 (NEVILLE, D.M., et al.) 15 August 2000.

KREITMAN, R.J., et al. Recombinant Single-Chain Immunotoxins Against T and B Cell Leukemias. *Leukemia and Lymphoma* 1994; 13:1-10.

KREITMAN, R.J., et al. Targeting *Pseudomonas* exotoxin to heamatologic malignancies. *Cancer Biology* 1995; 6:297-306.

KUSSIE, P.H., et al. A Single Engineered Amino Acid Substitution Changes Antibody Fine Specificity. *J. Immunology* 1994; 152:146-152.

CHEN, C., et al. Enhancement and destruction of antibody function by somatic mutation: unequal occurrence is controlled by V gene combinatorial associations. *The EMBO J.* 1995; 14(12):2784-2794.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims: NOTE: the Roman numerals correspond to those used to identify Appellant's arguments.

I) Claims 51-53 (as originally applied to Claims 31-33) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Appellant was in possession of a polypeptide encoded by one or more nucleotide sequences which hybridize to SEQ ID NO:2. Said hybridizing nucleotide sequences encompass a virtually unlimited number of polynucleotides, only one of which, SEQ ID NO:2, has been disclosed. Likewise, the specification provides an insufficient written description of antibodies having a variable region which is at least 99% identical to the variable region of UCHT-I and is at least 95% as effective on a molar basis in competing with UCHT-1. No such variants of the UCHT-1 antibody are disclosed in the specification. Given the essentially unlimited number of antibodies encoded by a virtually unlimited number of polynucleotides encompassed by the claims, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

II) Claims 50-51 (as originally applied to Claims 31-33) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a recombinant immunotoxin polypeptide consisting of the polypeptide encoded by the nucleotide sequence of SEQ ID NO:2, does not reasonably provide enablement for:

a recombinant immunotoxin polypeptide comprising an antibody having a variable region which is at least about 90% identical to the variable region of UCHT-1 and is at least about 90% as effective as UCHT-1 for binding human CD3.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

It is well established that changes in the amino acid sequence of the variable region of an antibody create new antibodies with highly unpredictable binding characteristics. See, for example Kussie et al. (1994, Table I) which teaches that the substitution of a single amino acid can totally ablate antigen binding. As a further demonstration of the unpredictability of substituted or mutated antibodies, see Chen et al. (1995). The reference again teaches that the substitution of a single amino acid can totally ablate antigen binding (Figure 1), however, the reference additionally teaches that the same substitution in closely related antibodies can have opposite effects. The authors compared the effects of identical substitutions in related antibodies D16 and T15, and as shown in Figure 3, some substitutions increased antigen binding in one antibody while ablating it in the other. The

reference serves to demonstrate the highly unpredictable nature of substituted antibodies and thus, the highly unpredictable nature of the antibody of the instant claims. Given said unpredictability, significant direction would be required to make and use the instant invention as claimed. However, the specification discloses just a single recombinant immunotoxin antibody (other than that encoded SEQ ID NO:2) with a single mutation in a residue outside the CDR antigen binding domains. Said disclosure is insufficient to enable the unlimited number of immunotoxins encompassed by Claim 50 (previously Claim 33).

*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In view of the quantity of experimentation necessary, the lack of sufficient working examples encompassing the entirety of the claimed methods, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

V) Claims 35-54 (as originally applied to Claims 1-7, 9-16, 29-30, and 33-34) are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,103,235 (2000) in view of Kreitman et al. (1995) and Kreitman et al. (1994).

The '235 patent teaches a recombinant immunotoxin polypeptide (RIP) comprising a single chain Fv (which is an $F_{ab}$ fragment) anti-human UCHT-1 CD3εγ binding domain and a diphtheria toxin (DT) (an ADP-ribosylating exotoxin) (see entire document, particularly column 19 lines, 21-30). The reference

further discloses a RIP pharmaceutical composition comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a $V_L$ - L - $V_H$ - C - exotoxin conformation (see particularly Figure 12).

The reference teachings differ from the claimed invention in that they do not teach the use of PE38 as the ADP-ribosylating exotoxin in the RIP construct.

Kreitman et al. (1995) teaches immunotoxic antibody - PE38 fusion proteins and antibody - PE40 fusion proteins (see particularly, Figure 1). The reference further teaches that the PE 38 and PE40 immunotoxins are functionally interchangeable (see particularly Figure 2A).

Kreitman et al. (1994) teaches immunotoxic antibody - PE40 fusion proteins and immunotoxic antibody - DT fusion proteins, and that they are functionally interchangeable (see particularly, Figure 2 and Table 2).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a pharmaceutical composition comprising a RIP comprising a single chain Fv (which is an $F_{ab}$ fragment) anti-human UCHT-1 CD3$\varepsilon\gamma$ binding domain, further comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a $V_L$ - L - $V_H$ - C - exotoxin conformation (the polypeptide of SEQ ID NO:1, encoded by the nucleotide of SEQ ID NO:2), as taught by the '235 patent substituting the PE38 exotoxin for the DT exotoxin, as taught by

Kreitman et al. (1994 and 1995). One of ordinary skill in the art would have been motivated to make said substitution because PE38 exotoxin was a well-known equivalent for PE40 exotoxin which was a well-known equivalent for the DT exotoxin disclosed in the '235 patent, as demonstrated by Kreitman et al. (1995 and 1994). The substitution of known equivalents is considered obvious (see MPEP 2164.06) and one of ordinary skill in the art would have a reasonable expectation of success in making said substitution. Note that the claim limitation of a PE mutant having ADP-ribosylating and translocation functions but substantially diminished cell-binding ability recited in Claim 1 merely comprises a functional characteristic of the PE38 mutant taught by Kreitman et al. (1995). Likewise, the claim limitations of claims 3-11, regarding the CD3 binding domain, e.g., an anti-CD3 binding fragment which binds an epitope on the CD3ε chain comprising a single chain Fv, are functional characteristics of the UCHT-1 antibody and thus characteristics of the UCHT-1 construct of the '235 patent.

**WITHDRAWN REJECTIONS**

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of Claim 50 under the under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

**(10) Response to Argument**

I) Appellant indicates that the claims have been amended since the original rejection. However, "As understood by Appellants, there are two aspects to the present ground of rejection, the first concerns the 90% identity language and the second concerns the 90% effectiveness language."

These are precisely the aspects necessitating the rejection.

Appellant argues that in view of *Enzo* the specification provides sufficient function and structure to describe the claimed invention.

It remains the Examiner's position that while the specification does provide a function for the claimed recombinant immunotoxin, it fails to provide an adequate structure. Indeed, the claimed product is essentially described by function alone, i.e., that it "is at least about 90% as effective on a molar basis in competing with UCHT-1 for binding to human CD3 antigen". Other than the requirement that the claimed product "have at least one sequence segment of at least five amino acids of human origin" the claims recite essentially no structural requirements and as set forth in the office actions no such requirements are disclosed in the specification. The specification discloses just a single construct comprising a single variation which cannot be considered sufficient written description for the essentially unlimited number of products that might be encompassed by the instant claims.

Appellant cites Example 9 of the Written Description Guidelines and argues that "it is Appellants' position that in the context of *Enzo* and Claims 51-53, 90% identity is analogous to hybridization under stringent conditions.

It is the Examiner's position that 90% identity is *not* analogous to hybridization under stringent conditions. DNA hybridization occurs under experimental conditions wherein the structure of the DNA is artificially altered by varying both the temperature and the salt content of the hybridizing solution. And note that said conditions are readily controlled by the experimenter. Such conditions are *not* applicable in varying the amino acid composition of a protein wherein three dimensional structure, and thus the protein's function (in this instance binding specificity), is *not* under the experimenter's control but is subject only to the experimenter's best guess.

Appellant argues that the specification teaches a method for determining sequence identity.

It remains the Examiner's position that said teaching provides nothing in regard to a written description of the claimed products. Indeed, said argument would be more appropriate in traversal of a rejection for lack of enablement.

II) Appellant argues that the specification is enabling and that while the required experimentation may be labor-intensive it is not undue.

It remains the Examiner's position that the functional limitations of the claims remain insufficient as the limitations continue to comprise only a trial-and-error sort of enablement, i.e., if an antibody is tested and it comprises the claimed limitations, then it is encompassed by the claims. It remains the Examiner's position that this limited guidance cannot be considered to be enabling. Also consider the number of possible mutations/additions/subtractions to be evaluated by this trial-and-error approach. The $V_L$ of the claimed product comprises approximately 109 amino acids. The $V_H$ of the claimed product comprises approximately 122 amino acids. Accordingly, for just a single mutation/addition/subtraction the $V_L$ might comprise $109^{20}$ different proteins and the $V_H$ $122^{20}$. Add to this the fact that the $V_L$ might comprise 1, 2, 3, …,10 individual mutations/additions/subtractions and the $V_H$ an additional 1, 2, 3, …,12 individual mutations/additions/subtraction and the number of possible mutated immunotoxins encompassed by the claims becomes almost incalculable. Given that the specification, and Appellant's arguments, teach only a trial-and-error approach, the amount of experimentation necessary establish the immunotoxins of the claims would indeed be undue.

V) Appellant argues a lack of motivation to combine the "bits and pieces" of the claimed immunotoxin.

The "bits and pieces" referred to by Appellant comprise precisely an antibody and a toxin. In combination they comprise an immunotoxin. The prior art establishes that the PE toxin of the claimed immunotoxin is an equivalent of the DT toxin of the

prior art. Accordingly, the substitution of PE toxin for DT toxin in an immunotoxin is obvious.

Appellant argues that Kreitman et al. (1994) does not teach that PE40 immunotoxins and DT immunotoxins are interchangeable. Appellant further argues that the effectiveness of any given immunotoxin combination could not be predicted.

The reference teaches that all of the immunotoxins were toxic. While toxicity in any particular context, i.e., for any particular use, might vary, the reference even goes so far as to discus the "**Variables affecting activity of recombinant immunotoxins**" (page 7). Accordingly, the skilled artisan might also be motivated to substitute PE toxin for DT toxin in an immunotoxin product simply to see if the resulting immunotoxin might be more toxic in any particular context. Said motivation alone would be sufficient to render the claimed products obvious.

Appellant cites Batra et al. (1991) as teaching that the effectiveness of immunotoxins might vary and concludes "one skilled in the art having the prior art before him could not *a priori* reasonably predict the effectiveness for a particular use of an anti-CD3-PE based immunotoxin with the knowledge that an anti-CD3-DT based immunotoxin is effective for that use".

Given that the claimed invention is a product, motivation need only be established to produce said product. Additionally, just a reasonable expectation of success in using said product for just a single purpose need also be established. In the

instant case, there is no reasonable argument presented that there would be *no* expectation of success in using the PE immunotoxin of instant claims in view of the prior art, i.e., there is no argument that the prior art indicates that an anti-CD3-PE immunotoxin would *not* be toxic. The only question is whether or not, in any given context, would a PE immunotoxin be more or less toxic than a DT immunotoxin. Thus, this is not an "obvious to try situation" because there is no question that the product will function. Accordingly, if for no other reason, the immunotoxin of the instant claims would be obvious in view of the prior art as, at the very least a substitute, and possibly a superior, product.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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10/24/02
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